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Foetal and Maternal Magnesium Metabolism: Effect of Magnesium Deficiency and Isoproterenol

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Dedicated to Professor Dr. Dr. Ernst Schütte on the occasion of his 75th birthday

Summary: Pregnant rats were fed diets with an Mg^{2+} content of 40, 12, 6 and 3 mmol/kg from day 10–19 of pregnancy. There was a linear correlation of non-protein bound Mg^{2+} between foetal and maternal serum, between amniotic fluid and maternal serum, and between foetal serum and amniotic fluid, the ratios being 2.7, 2.0 and 1.3 respectively, indicating active transport of Mg^{2+} up to a constant concentration gradient by the placenta. In hearts, increases of Na^+ and Ca^{2+} , and decreases of Mg^{2+} and K^+ were observed only in the group receiving the lowest Mg^{2+} supply.

After i. v. injection of $MgCl_2$ to pregnant rats, Mg^{2+} was slowly transported from maternal to foetal serum and more slowly into the amniotic fluid.

The effect of isoproterenol on cardiac electrolyte content in pregnant rats was less than in non-pregnant rats, and the effect of isoproterenol in foetal rats was smaller than in maternal rats. These results are explained by inactivation of isoproterenol in the placenta, by the small diaplacental transport of isoproterenol and by a smaller isoproterenol-stimulation of foetal cardiac adenylate cyclase.

Foetaler und maternaler Magnesium-Stoffwechsel: Beeinflussung durch Magnesium-Mangel und durch Isoproterenol

Zusammenfassung: Schwangere Ratten wurden vom Tag 10 bis 19 der Schwangerschaft mit einer Diät gefüttert, die 40, 12, 6 und 3 mmol/kg Mg^{2+} enthielt. Es ergab sich für das nicht an Protein gebundene Mg^{2+} eine lineare Korrelation zwischen foetalem und mütterlichem Serum, zwischen Amnionflüssigkeit und mütterlichem Serum sowie zwischen foetalem Serum und Amnionflüssigkeit. Das Verhältnis der Mg^{2+} Konzentrationen betrug für die einzelnen Korrelationen 2,7; 2,0 und 1,3. Daraus ergibt sich, daß Mg^{2+} bis zu einem konstanten Konzentrationsgradienten angereichert wird.

Nur in der Gruppe mit der geringsten Mg^{2+} -Zufuhr waren im Herzen der Na^+ - und Ca^{2+} -Gehalt erhöht und der Mg^{2+} - und K^+ -Gehalt erniedrigt.

Nach intravenöser Injektion von $MgCl_2$ wurde Mg^{2+} nur sehr langsam vom mütterlichen zum foetalen Serum und noch langsamer in die Amnionflüssigkeit transportiert.

Die Wirkung von Isoproterenol auf den Elektrolytgehalt des Herzens war bei schwangeren Ratten wesentlich geringer als bei nicht schwangeren. Bei den Foeten wirkte Isoproterenol noch schwächer als bei den Müttern. Dieses Ergebnis läßt sich mit einer Inaktivierung des Isoproterenols in der Placenta, mit der geringen Placentalpassage von Katecholaminen und mit der geringeren Stimulierbarkeit der foetalen Adenylatcyclase durch Isoproterenol erklären.

Introduction

In early stages of foetal development in rats (1, 2) and chicken (3), the Mg^{2+} concentration is higher in foetal than in maternal serum and decreases with time. Shortly before birth, the serum Mg^{2+} concentration is still higher in foetal than in maternal rat serum (1, 2, 4). During foetal development, the protein concentration in foetal serum increases. However, shortly before birth the protein concentration is still lower in foetal than in maternal rat serum (1, 2). Depending on the protein concentration, approximately one third of Mg^{2+} in serum is bound to protein particularly to albumin (5). Thus, the ratio of non-protein bound Mg^{2+} in foetal to that in maternal serum is still higher than the ratio of total serum Mg^{2+} . Obviously, the placenta is able to enrich Mg^{2+} at its foetal site.

When the maternal Mg^{2+} supply is insufficient, the maternal serum Mg^{2+} concentration decreases. Below a threshold of 0.6 mmol/l (6), foetal retardation and resorption (6, 7, 8), foetal anaemia (8), malformation (7, 8) and a higher mortality of the newborns (7) have been observed, corresponding to the degree of Mg deficiency. A mild Mg deficiency in combination with foetal hypotrophy has also been found in some pregnant women particularly during the second half of pregnancy (9). We therefore produced varying degrees of Mg deficiency in pregnant rats from day 10 to 19 and studied the Mg^{2+} concentration in serum and amniotic fluid, and the electrolyte contents of hearts and livers from the foetal and maternal rats.

A knowledge of the electrolyte metabolism of foetal hearts in Mg deficiency is especially interesting because it permits an assessment of the risk of foetal heart damage during tocolysis with β -agonists; β -agonists induce a reduction of Mg^{2+} and an increase in Ca^{2+} and Na^+ content in the myocardium followed by necroses of heart muscle cells (10, 11). These harmful β -adrenergic effects can be prevented by a previous Mg^{2+} supplementation (10, 11). On the other hand, the effects of Mg deficiency and isoproterenol on cardiac electrolytes have been shown to be additive (12). Therefore, we also compared the effect of isoproterenol on the electrolyte contents of foetal and maternal hearts.

Materials and Methods

Female Wistar rats weighing 200 g were maintained under a 12 hour light-dark cycle and at a temperature of about 20 °C. Virgin females were mated from 8–10 a.m. and impregnated females were identified by the presence of copulatory plugs. This day was designated as day 0 of gestation. Up to day 10, the rats were fed with Altromin (Mg content: 80 mmol/kg) and tap water ad libitum.

Experimental design

I. Experiment

From day 10–19 of pregnancy, the rats were fed with a synthetic Mg deficient diet (Ssniff, Soest, FRG); its composition has already been described (13). This diet (Ca^{2+} content: 250 mmol/kg) was supplemented with $MgCl_2$ to a final Mg^{2+} content of 40 mmol/kg, 12 mmol/kg, 6 mmol/kg, and 3 mmol/kg (no supplementation). The rats in each group (number as indicated in tab. 1) were fed with this diet and distilled water ad libitum.

On day 19, under nembutal anesthesia (50 mg/kg s.c.), amniotic fluid was sampled. Blood was taken from the foetal hearts by means of capillaries and from the mother. The capillaries were closed at one end and centrifuged for 5 min at 1300 g. Hearts and livers were removed, cleaned in cold sucrose (100 g/l), frozen in liquid nitrogen and freeze-dried. Foetal livers and maternal tissues were pulverized. Foetal serum samples from the same mothers were pooled for determination of Mg^{2+} , Ca^{2+} and protein.

II. Experiment

On day 19, under nembutal anesthesia, the arteria and vena renalis were ligated in those pregnant rats fed a diet containing 40 mmol/kg Mg^{2+} or 6 mmol/kg Mg^{2+} from day 10–19. Thereafter, the rats were intravenously injected with 0.5 ml 150 mmol/l $MgCl_2$. At various times up to 200 min p.i. maternal and foetal blood and amniotic fluid were taken.

III. Experiment

Normally fed pregnant rats on day 20 of pregnancy were subcutaneously injected with 3 mg/kg isoproterenol. At 2, 4 and 6 h p.i., under nembutal anesthesia, blood, amniotic fluid, livers and hearts were taken from the maternal and foetal rats and treated as described above.

IV. Experiment

Normally fed male Wistar rats weighing 250 g were s.c. injected 4 times every other day with 3 mg oestradiol, 3 mg progesterone and with both in combination. After seven days they were injected with 3 mg/kg isoproterenol. Six hours after injection of isoproterenol the rats were killed.

Analytical procedures

Protein contents were measured in 10 μ l of foetal and 5 μ l of maternal serum or 10 μ l amniotic fluid according to Lowry et al. (14). For the determination of Mg^{2+} and Ca^{2+} , 100 μ l and 50 μ l respectively of amniotic fluid or serum were diluted with 1.8 ml trichloroacetic acid (50 g/l) containing 1 g/l La^{3+} and measured in an atomic absorption spectrophotometer (Perkin-Elmer, model 300). Phosphate was determined according to Fiske & Subbarow (15). Concentrations of non-protein bound Mg^{2+} and Ca^{2+} in serum were calculated according to l.c. (16, 17).

For the determination of tissue electrolytes, 3–4 freeze-dried foetal hearts and 20 mg of the other freeze-dried tissues were ashed overnight in a Low Temperature Asher (Fa. Tracerlab). The ashes were dissolved in 3 ml 0.1 mol/l HCl. For the determination of Ca^{2+} , 100 μ l were diluted with 200 μ l Millipore water. 20 μ l in quadruplicates were injected into a graphite furnace and measured according to the Perkin Elmer manual.

For the determination of Mg^{2+} , 1 ml was diluted with 2 ml 1 g/l La^{3+} in 0.1 mol/l HCl and measured by flame atomic absorption spectrophotometry. For the determination of Na^+ and K^+ , 0.5 ml were diluted with 0.5 ml 30 mmol/l LiCl and measured in a flame photometer (Beckman). All solutions were made with Millipore water.

However, other Ca^{2+} binding substances e.g. phosphate must be considered. In normal foetal and maternal serum we found a phosphate concentration of 4.9 ± 0.4 and 2.4 ± 0.1 mmol/l respectively. Other authors also found a higher phosphate concentration in foetal serum (2). Mg deficiency had no effect on the phosphate concentration in serum.

Using the Mg^{2+} -phosphate binding constant of 33 l/mol (18), it can be calculated that in maternal rat serum maximally 8% and in foetal serum maximally 16% of non-protein bound Mg^{2+} are bound to phosphate. When binding of Ca^{2+} to phosphate is taken into account, the effect of phosphate on Mg^{2+} binding is somewhat lower. Taking this binding into account, the foetal-maternal Mg^{2+} gradient, which amounts to 2.7 for non-protein bound Mg^{2+} , would be maximally reduced to 2.5 for free Mg^{2+} . Therefore, one can conclude that in the placenta there is a specific Mg^{2+} transport system, Ca^{2+} being unaffected.

To test the Mg^{2+} transporting capacity of the placenta, the maternal serum Mg^{2+} concentration was elevated by i. v. injection of MgCl_2 . Thirty minutes after injection of 0.5 ml 0.15 mol/l MgCl_2 , the total Mg^{2+} in maternal serum of normally fed rats was increased to 4.3 ± 0.2 mmol/l, and thereafter decreased continuously; after 200 min, the maternal serum Mg^{2+} concentration was 2.3 ± 0.2 mmol/l. The simultaneously measured foetal serum Mg^{2+} concentration increased only slowly. During the experimental period up to 200 min no steady state was reached. When the non-protein bound Mg^{2+} concentration was calculated and plotted (fig. 2) it was apparent that the foetal-maternal Mg^{2+} concentration gradient was different from that under physiological conditions. After injection of MgCl_2 , the free Mg^{2+} concentration is higher in maternal than in foetal serum. Therefore, under these experimental conditions, net placental Mg^{2+} transport occurred along the concentration gradient and was low. When the same experiment was done with Mg-deficient rats the same result was obtained although at a lower Mg^{2+} concentration. In both experiments, the increase of foetal serum Mg^{2+} amounted to 0.08 mmol/l \times hour.

In lymphoma cells (19) Mg^{2+} transport can be inhibited by isoproterenol. Therefore, foetal-maternal Mg^{2+} distribution was measured 2, 4 and 6 hours after injection of 3 mg/kg isoproterenol to pregnant rats. As can be seen from table 2, the foetal Mg^{2+} serum concentration was reduced, particularly 2 h after injection, and increased again later. Maternal serum Mg^{2+} behaved inversely to foetal serum Mg^{2+} . Maternal serum Mg^{2+} was elevated by isoproterenol, due to Mg^{2+} release from the maternal heart, and

Tab. 2. Protein, Mg^{2+} and Ca^{2+} concentrations in maternal and foetal serum and in amniotic fluid of normally fed rats 2, 4, and 6 hours after s.c. injection of 3 mg/kg isoproterenol. s. legend tab. 1. Mean \pm SEM. Significance when indicated: ^a $p < 0.001$ ^b $p < 0.01$

Time after isoproterenol (h)	n	Maternal serum				Foetal serum				Amniotic fluid			
		Protein (g/l)	[Mg] _{total} (mmol/l)	[Mg ²⁺] _{h.p.} (mmol/l)	[Ca] _{total} (mmol/l)	[Ca ²⁺] _{h.p.} (mmol/l)	Protein (g/l)	[Mg] _{total} (mmol/l)	[Mg ²⁺] _{h.p.} (mmol/l)	[Ca] _{total} (mmol/l)	[Ca ²⁺] _{h.p.} (mmol/l)	Protein (g/l)	[Mg] _{total} (mmol/l)
Control	6	61 \pm 3	0.83 \pm 0.04	0.56 \pm 0.03	2.64 \pm 0.11	1.30 \pm 0.08	27 \pm 2	1.56 \pm 0.10	1.33 \pm 0.08	2.18 \pm 0.07	1.50 \pm 0.12	1 \pm 1	0.99 \pm 0.07
2	6	61 \pm 3	1.35 \pm 0.06 ^a	0.92 \pm 0.06 ^a	2.62 \pm 0.05	1.30 \pm 0.08	21 \pm 3	1.22 \pm 0.04 ^b	1.10 \pm 0.09	2.28 \pm 0.03	1.66 \pm 0.10	1 \pm 1	0.99 \pm 0.09
4	3	57 \pm 3	1.14 \pm 0.05 ^b	0.80 \pm 0.06 ^b	2.44 \pm 0.06	1.20 \pm 0.09	20 \pm 3	1.33 \pm 0.05	1.20 \pm 0.07	2.18 \pm 0.05	1.68 \pm 0.11	2 \pm 1	1.08 \pm 0.03
6	3	59 \pm 2	0.98 \pm 0.01 ^b	0.68 \pm 0.05	2.40 \pm 0.08	1.18 \pm 0.07	23 \pm 2	1.40 \pm 0.05	1.25 \pm 0.09	2.16 \pm 0.12	1.62 \pm 0.13	2 \pm 1	1.10 \pm 0.02
													2.62 \pm 0.09
													2.56 \pm 0.17
													2.75 \pm 0.07
													2.79 \pm 0.02

probably by foetal Mg^{2+} diffusing from foetal serum to maternal serum along the concentration gradient. The latter conclusion is supported by the fact that isoproterenol reduced foetal serum Mg^{2+} but did not change the foetal cellular Mg^{2+} content (s. below, tab. 4). Ca^{2+} and protein concentrations in maternal and foetal serum were not affected by isoproterenol.

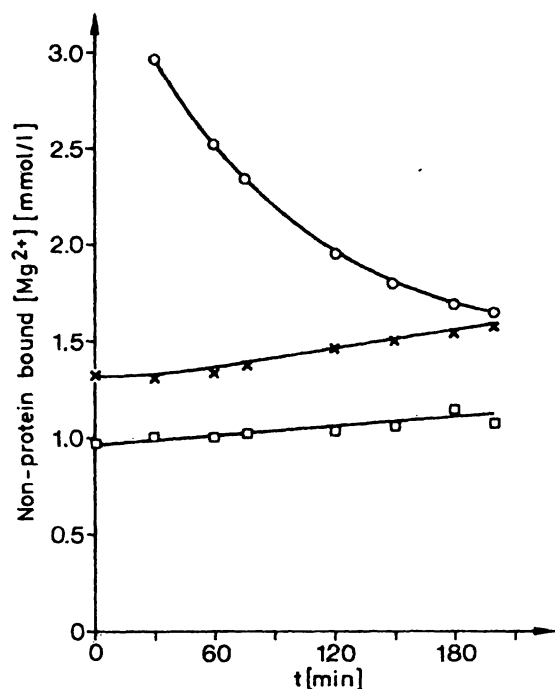


Fig. 2. Non-protein bound Mg^{2+} in maternal (O) and foetal (x) serum and in amniotic fluid (□) at different times after intravenous injection of 0.5 ml 0.15 mmol/l MgCl_2 to pregnant rats after ligation of renal veins and arteries.

Amniotic fluid (tab. 1, 2)

Since the protein and phosphate contents in amniotic fluid are very low ($[\text{P}_i] = 0.9 \pm 0.1$ mmol/l), total Mg^{2+} and total Ca^{2+} concentrations are only somewhat higher than the concentration of free Mg^{2+} and free Ca^{2+} . When the Mg^{2+} content in the diet was reduced, the total Mg^{2+} concentration in the amniotic fluid was also reduced. As in the case of foetal serum, the Mg^{2+} concentration in the amniotic fluid also exhibited a linear correlation when the Mg^{2+} concentration in amniotic fluid was plotted versus non-protein bound Mg^{2+} in maternal serum, the Mg^{2+} concentration in amniotic fluid being always twice that of non-protein bound Mg^{2+} in maternal serum (fig. 3). As the phosphate concentration in amniotic fluid is lower than in maternal serum, the effect of phosphate on Mg^{2+} binding can be neglected. When the Mg^{2+} concentration in amniotic fluid was correlated with the concentration of non-protein bound Mg^{2+} in foetal serum, a linear correlation was again obtained; the concentration of non-protein bound Mg^{2+} in foetal serum is about 30% higher than total Mg^{2+} in amniotic fluid (fig. 4).

The linear relationships indicate that there is a steady state of Mg^{2+} distribution between these fluids in the Mg deficiency experiment. After injection of MgCl_2 , Mg^{2+} uptake into the amniotic fluid was still slower than Mg^{2+} uptake into foetal serum (fig. 2). In normal and Mg deficient rats the increase of Mg in the amniotic fluid amounted to $0.03 \text{ mmol/l} \times \text{h}$. After injection of 3 mg/kg isoproterenol, the Mg^{2+} concen-

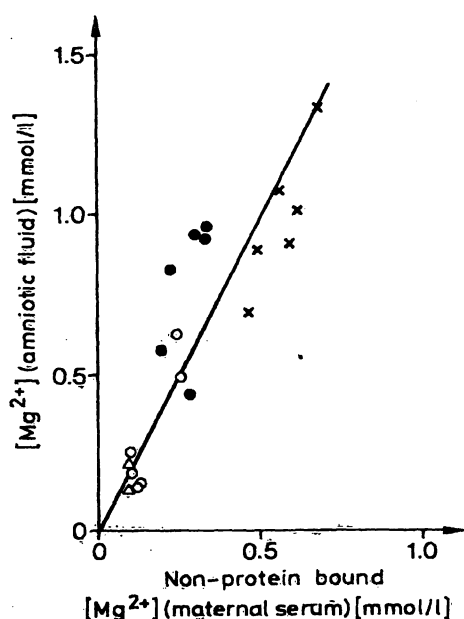


Fig. 3. Correlation of non-protein bound Mg^{2+} in amniotic fluid and maternal serum. Symbols as in fig. 1.

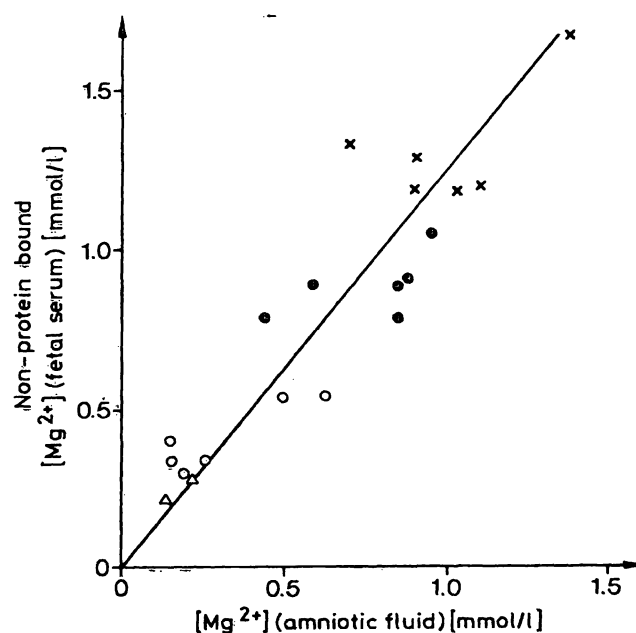


Fig. 4. Correlation of non-protein bound Mg^{2+} in foetal serum and amniotic fluid. Symbols as in fig. 1.

tration in amniotic fluid was not significantly changed. The Mg^{2+} concentration gradient between foetal serum and amniotic fluid was reduced from 1.35 to 1.1 (from tab. 1), due to the decrease of Mg^{2+} in foetal serum.

Interestingly, because of the low protein and phosphate content, the non-protein bound Ca^{2+} concentration in the amniotic fluid is higher than in foetal and maternal serum. As yet, we have no explanation for this observation. In Mg deficiency and after injection of $MgCl_2$ or isoproterenol, the Ca^{2+} concentration in the amniotic fluid was not changed.

Tissue electrolyte contents (tab. 3, 4)

On a dry weight basis, the electrolyte contents are higher in foetal than maternal tissues with the exception of Ca^{2+} in foetal liver.

As Mg^{2+} and K^+ have a predominantly intracellular location, foetal liver and myocardial cells have a higher content of Mg^{2+} and a higher intracellular K^+ concentration. In earlier experiments with foetal rat liver (1) we showed that although there was a higher total Mg^{2+} content, the concentration of free Mg^{2+} was not enhanced in foetal liver, indicating a higher amount of bound Mg^{2+} . This effect can be explained by the greater number of ribosomes in foetal than in maternal tissues and by the Mg^{2+} binding properties of these organelles.

The higher content of the preponderantly extracellularly localized Na^+ may be due to the higher extracellular fluid volume in foetal tissues. After feeding the diets with low Mg^{2+} contents, Na^+ and Ca^{2+} contents in maternal foetal heart were elevated, and K^+ and Mg^{2+} contents were reduced. The effect was only significantly expressed in the group fed with 3 mmol/kg Mg^{2+} . In liver the effect of Mg deficiency is smaller than in heart (20). Thus, no effect was observed in maternal liver, owing to the short experimental period, whereas foetal livers showed similar (but non-significant) changes to those observed in the heart (tab. 3).

In foetal tissues the Mg deficiency-induced alterations in electrolyte content were more pronounced than in maternal tissues. This can be explained by the higher growth rate of foetal tissues, because the Mg deficiency-induced alterations in electrolyte content depend on growth rate (20).

After injection of 3 mg/kg isoproterenol Na^+ and Ca^{2+} contents in the maternal hearts were increased, whereas the Mg^{2+} content was decreased 2 hours p.i. and was normalized thereafter. The K^+ content was not significantly changed. Thus the alterations are qualitatively similar to the alterations of electrolyte content, as found in experiments with male rats (12). However, the effects of 3 mg/kg isoproterenol in pregnant rats were much smaller than those observed for the same dose in male rats. In the foetal hearts the effect of isoproterenol was even smaller than in maternal hearts (tab. 4).

Tab. 3. Electrolyte content in maternal and foetal heart and liver after feeding a diet of different Mg^{2+} content from day 10 to 19 of pregnancy. Mean \pm SEM, n = number of pregnant rats. Significance ^a p < 0.001 ^b p < 0.01 ^c p < 0.05

Mg ²⁺ in diet	n	Mg ²⁺ (mmol/kg dry weight)	Ca ²⁺ (mmol/kg dry weight)	Na ⁺ (mmol/kg dry weight)	K ⁺ (mmol/kg dry weight)	Mg ²⁺ (mmol/kg dry weight)	Ca ²⁺ (mmol/kg dry weight)	Na ⁺ (mmol/kg dry weight)	K ⁺ (mmol/kg dry weight)
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Maternal heart					Foetal heart				
40	6	38.0 ± 0.3	2.6 ± 0.1	142 ± 4	347 ± 8	41.9 ± 0.6	4.6 ± 0.3	218 ± 10	468 ± 8
12	6	38.0 ± 1.1	2.9 ± 0.1	141 ± 5	328 ± 9	42.2 ± 0.7	4.6 ± 0.4	215 ± 8	459 ± 6
6	6	37.6 ± 0.9	2.9 ± 0.1	137 ± 4	327 ± 5	40.1 ± 0.9	5.0 ± 0.3	244 ± 9	455 ± 8
3	4	34.1 ± 1.0 ^b	3.2 ± 0.9	155 ± 3 ^c	296 ± 4 ^a	36.8 ± 1.2 ^c	6.5 ± 0.9	249 ± 8 ^c	382 ± 34 ^c
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Maternal liver					Foetal liver				
40	6	31.4 ± 0.6	3.0 ± 0.2	69 ± 3	355 ± 12	38.2 ± 1.0	2.4 ± 0.3	147 ± 6	451 ± 20
12	6	31.8 ± 0.5	3.2 ± 0.1	68 ± 1	354 ± 7	38.7 ± 0.8	2.6 ± 0.2	152 ± 11	472 ± 24
6	6	31.2 ± 1.0	3.2 ± 0.1	71 ± 3	351 ± 9	37.7 ± 1.7	2.4 ± 0.1	168 ± 3	465 ± 25
3	4	31.2 ± 2.3	3.0 ± 0.2	75 ± 6	359 ± 17 ^a	34.1 ± 1.5	2.6 ± 0.3	171 ± 8	431 ± 25
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Tab. 4. Electrolyte content of maternal and foetal heart 2, 4 and 6 hours after s.c. injection of 3 mg/kg isoproterenol. Mean \pm SEM. n = number of pregnant rats.
Significance when indicated: ^a p < 0.001 ^b p < 0.01 ^c p < 0.05.

Time after isoproterenol (h)	n	Maternal heart				Foetal heart			
		Mg ²⁺	Ca ²⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Na ⁺	K ⁺
		(mmol/kg dry weight)				(mmol/kg dry weight)			
Control	6	38.0 \pm 0.3	2.6 \pm 0.1	142 \pm 4	374 \pm 8	41.9 \pm 0.6	4.6 \pm 0.3	218 \pm 10	468 \pm 8
2	6	34.3 \pm 0.4 ^a	3.4 \pm 0.2 ^b	183 \pm 10 ^b	342 \pm 5	43.6 \pm 1.0	5.7 \pm 0.3 ^c	232 \pm 9	483 \pm 7
4	3	36.6 \pm 1.4	3.2 \pm 0.2 ^c	170 \pm 3 ^a	367 \pm 9	43.6 \pm 1.0	5.4 \pm 0.3	192 \pm 8	477 \pm 18
6	3	37.0 \pm 0.9	3.7 \pm 0.1 ^a	187 \pm 7 ^a	370 \pm 8	42.0 \pm 1.6	5.5 \pm 0.3	212 \pm 16	482 \pm 17

Following the injection of isoproterenol, maternal and foetal livers showed no alteration of electrolyte contents (not shown). This result is in agreement with the finding of others (21), demonstrating that isoproterenol has a rather cardiospecific effect.

The very low effect of isoproterenol in pregnant rats was not caused by the changed hormonal situation in pregnancy. Injection of isoproterenol into non-pregnant female rats, male rats and male rats pretreated with oestradiol, progesterone and oestradiol-progesterone in combination produced the same alterations in cardiac electrolyte content as described for male rats (12), particularly the drastic increase in cardiac Ca²⁺ content from 2.8 in normal rats to 9 mmol/kg dry weight.

Therefore, one can conclude, that in pregnant rats the placenta was responsible diminishing the effect of isoproterenol on the maternal myocardial electrolyte content.

Discussion

Our results indicate that there is an active transport of Mg²⁺ in the placenta. It seems reasonable to correlate the placental Mg²⁺ transport with the syncytium covering the foetal capillaries. The syncytium contains a brush border like intestinal epithelial cells and may be able to transport Mg²⁺.

This function may be in analogy to the Mg²⁺ transport by the epithelial layer of the chorioid plexus, resulting in an increased Mg²⁺ concentration in the cerebrospinal fluid (22). However, the direction of Mg²⁺ transport would be opposite in these two epithelial layers.

Placental Mg²⁺ transport operates with unchanged efficiency during Mg deficiency, always producing the same Mg²⁺ concentration gradient over a wide range of free Mg²⁺ concentrations (0.1 to 0.6 mmol/l) in serum. Therefore, maternal serum Mg²⁺ concentrations can be used as an index of foetal serum Mg²⁺ concentrations. However, there is disagreement on the concentration range. Dancis et al. (4) found that the Mg²⁺ concentration gradient broke down in Mg deficiency. It is possible that the latter result was due to by foetal death.

The capacity of net Mg²⁺ transport in the placenta is rather limited. After elevation of maternal serum Mg²⁺ concentration by i.v. MgCl₂ injection, foetal Mg²⁺ concentration increased only slowly. In this experiment the maternal serum Mg²⁺ concentration, increased by i.v. MgCl₂ injection, decreased rapidly. Since renal excretion was eliminated and foetal Mg²⁺ uptake was rather slow, the injected Mg²⁺ must have been taken up by maternal tissues, particularly by maternal bone. Bone contains about 50% of total body Mg²⁺, and Mg²⁺ in bone is in equilibrium with extracellular Mg²⁺ (5). In agreement with this conclusion, injected ²⁸Mg²⁺ was rapidly removed from maternal serum with a similar time course and was rapidly taken up particularly by maternal bone (23) (essentially by isotopic ²⁸Mg²⁺-²⁴Mg²⁺-exchange).

In agreement with the slow net placental Mg²⁺ transport, ²⁸Mg²⁺ transport (exchange) to foetal serum was also limited. Immediately after i.v. injection, ²⁸Mg²⁺ activity in foetal serum reached an almost constant but low level (23). From this result one can conclude that the single ²⁸Mg²⁺ ion is transported rapidly across the placenta. However, the number of transported ²⁸Mg²⁺ ions was rather limited and ²⁸Mg²⁺ that had crossed the placenta was rapidly exchanged with foetal tissue Mg²⁺.

To define active placental Mg^{2+} transport, the electrical potential difference must be considered. The transplacental electrical potential difference amounted to 50 mV in sheep and to 70 mV in goats (foetus negative) (24). However, there was no concentration gradient between foetal and maternal serum for Na^+ and K^+ (4, 24, 25). There is no explanation for this effect. Considering the transplacental potential difference of 50–70 mV (foetus negative) and the Mg^{2+} concentration gradient, there should be an active Mg^{2+} transport from foetal to maternal serum if placental Mg^{2+} transport depends on the potential difference. However, it is possible that placental Mg^{2+} transport is independent of membrane potential.

Thus placental Mg^{2+} transport exhibits similar properties to cellular Mg^{2+} transport. Intracellular free Mg^{2+} concentration is also 2–3 times higher than extracellular free Mg^{2+} (20) and is probably independent of membrane potential.

Mg^{2+} transport by lymphoma cells (19) involves the β -receptor-adenylate cyclase complex. A similar effect may be involved in placental Mg^{2+} transport. After isoproterenol injection there was a transient decrease in foetal Mg^{2+} serum concentration.

This may be caused by a net flux of Mg^{2+} from foetal to maternal serum along the Mg^{2+} concentration gradient. It is possible that the inhibition of placental Mg^{2+} transport is caused by isoproterenol-stimulation of adenylate cyclase similar to that in lymphoma cells (19).

A striking effect is the drastically reduced action of isoproterenol in pregnant rats and in their foetuses after a single injection, in comparison with normal rats. Since pretreatment with corticoids alters isoproterenol-sensitivity (26) the effect of pretreatment with oestradiol and progesterone was tested. However, pretreatment with these hormones did not alter the isoproterenol response. Therefore, the placenta seems to reduce the isoproterenol action, probably by inactivating isoproterenol. The main biotransformation of isoproterenol is conversion to 3-O-methylisoproterenol by the action of catechol-O-methyltransferase (COMT) (27). As the placenta contains monoamine oxidase (MAO) and catechol-O-methyltransferase (for literature, see l.c. (28)), this reaction can occur. The physiological significance may be the protection of the foetus against harmful effects of catecholamines. This effect is supported by the very low diaplacental passage of catecholamines (28, 29, 30).

In late pregnancy in the myocardium of foetal rats and rabbits the number and affinity of β -adrenergic receptors are fully developed (31, 32, 33). However, maximal stimulation of adenylate cyclase by β -agonists in foetal hearts is lower than that of adult hearts (32, 34). The small isoproterenol response of the foetuses can be explained by the sum of these effects and by the higher foetal serum Mg^{2+} concentration. If applicable to humans, these results show that the foetus is more protected than its mother during tocolysis with β -agonists.

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